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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/875,849	09/08/1997	MICHAEL J. BRISKIN	LKS94-04A2	4411

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EXAMINER	
SCHWADRON, RONALD B	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/875,849	BRISKIN ET AL.	
	Examiner	Art Unit	
	Ron Schwadron, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *101,117 and 151* is/are withdrawn from consideration.

5)☐ Claim(s) *126-135* is/are allowed.

6)☒ Claim(s) *24-26,28-32,103,105-109,111-113,115,116,118-122,124,125,136-150 and 152-160* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 24-26,28-32,101,103,105-109,111-113,115-122,124-160.

1. Claims 24-26,28-32,103,105-109,111-113,115,116,118-122,124-150,152-160 are under consideration.

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 24-26,28-32,103,105-109,111-113,115,116,118-122,124,125,136-150,152-160 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants arguments have been considered and deemed not persuasive.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed inventions.

The instant claims encompass fusion proteins containing primate MAdCAMs from any primate as well as fusion proteins containing polymorphic or allelic variants of any primate (or human) MAdCAM wherein the proteins have a particular degree of amino acid sequence similarity as per recited in the claims. The specification discloses one amino acid sequence encoding macaque MAdCAM and two different amino acid sequences encoding human MAdCAM. With the exception of the aforementioned disclosed proteins, the skilled artisan cannot envision the detailed structure of the encompassed proteins and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. For example, there is no disclosure in the specification of chimp MAdCAM or baboon MAdCAM or spider monkey MAdCAM or gibbon MAdCAM or rhesus MAdCAM or polymorphic or allelic variants of said primate MAdCAMS. Regarding human

MAdCAM proteins and polymorphic or allelic variants of said human MAdCAM protein, there is no disclosure in the specification of human MAdCAM protein other than the two specifically disclosed protein sequences disclosed in the specification. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. In the instant application, the nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

In view of the aforementioned problems regarding description of the claimed invention, the specification does not provide an adequate written description of the invention claimed herein. See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1404-7 (Fed. Cir. 1997). In University of California v. Eli Lilly and Co., 39 U.S.P.Q.2d 1225 (Fed. Cir. 1995) the inventors claimed a genus of DNA species encoding insulin in different vertebrates or mammals, but had only described a single species of cDNA which encoded rat insulin. The court held that only the nucleic acids species described in the specification (i.e. nucleic acids encoding rat insulin) met the description requirement and that the inventors were not entitled to a claim encompassing a genus of nucleic acids encoding insulin from other vertebrates, mammals or humans, id. at 1240. The Federal Circuit has held that if an inventor is "unable to envision the detailed constitution of a gene so as to distinguish it from other materials. . .conception has not been achieved until reduction to practice has occurred", Amgen, Inc. v. Chugai Pharmaceutical Co, Ltd., 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991). Attention is also directed to the decision of The Regents of the University of California v. Eli Lilly and Company (CAFC, July 1997) wherein is stated:

"The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, as we have previously held, a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the

sequence of nucleotides that make up the cDNA." See Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606.

Regarding applicants comments about Example 14 from the Application of Guidelines, said Example deals with a specific claim that recites 95% identity to a particular recited sequence. None of the claims under consideration recite 95% identity to a particular recited sequence and therefore said Example is not germane to the claims under consideration. The instant claims encompass fusion proteins containing primate MAdCAMs from any primate as well as polymorphic or allelic variants of any primate MAdCAM wherein the proteins have a particular degree of amino acid sequence similarity as per recited in the claims. The specification discloses one amino acid sequence encoding macaque MAdCAM and two different amino acid sequences encoding human MAdCAM. With the exception of the aforementioned disclosed amino acid sequences, the skilled artisan cannot envision the detailed structure of the encompassed proteins (or fusion proteins containing said protein) and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. For example, there is no disclosure in the specification of chimp MAdCAM or baboon MAdCAM or spider monkey MAdCAM or gibbon MAdCAM or rhesus MAdCAM or polymorphic or allelic variants of said primate MAdCAMS. Regarding human MAdCAM and polymorphic or allelic variants of said human MAdCAM, there is no disclosure in the specification of human MAdCAM other than that specifically encoded by the two specific amino acid sequences disclosed in the specification. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. In the instant application, the amino acid itself or isolated protein is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

With the exception of fusion proteins containing SEQ. ID. NO:2 or 4 or 6, there is no disclosure of the amino acid sequences of other primates or primate polymorphic or allelic variants or non-naturally occurring mutants. Said sequences include two sequences derived from human and one sequence derived from a single species of macaque. According to WWW.blarg.com (found by searching Anthropoidea on DOGPILE search engine), there are 11 families, 52 genera and 181 species encompassed by the term primate. Thus, applicant has not provided a description of the

vast majority (eg. 179 of 181) of the amino acid sequences which encode primate MAdCAM. Furthermore, this figure does not even take into account naturally occurring polymorphic or allelic variants. If each species had multiple alleles or polymorphic variants than the potential number of MAdCAM sequences would vastly increase from the 181 sequences number. There is no disclosure in the specification of amino acid sequences encoding MAdCAM derived from the primates tufted ear marmoset, mantled howler, brown headed spider monkey, dusky titi, the patas monkey, savanna baboon, haunman langur, the black han gibbon, the bonobo, etc. Applicants disclosure is a minuscule fragment of the potential MAdCAMs derived from species encompassed by the term primate. Regarding applicants comments about claims that recite 55% similar, etc., in view of the fact that said claims do not specify what particular regions of the sequence are similar and do not specify the identity of the 45% nonsimilar portion, it is unclear as to how this provides a further description of the sequence encoding other primate variants. There is also no disclosure in the specification as to how many of the known primate sequences would be encompassed by the percent similarity language recited in the claims.

Regarding applicants comments, the US CAFC recently ruled in In Re Wallach et al. (CAFC 03-1327, available on the CAFC website) that written description for a nucleic acid sequence encoding a protein required a complete intact nucleic acid sequence encoding said protein or a complete intact amino acid sequence of a protein (from which the nucleic acid sequence could be derived). The court ruled that a partial amino acid sequence in itself (from which nucleic acid information could be derived) was insufficient to provide written description for the claimed nucleic acid. In the instant application, the claims encompass amino acids for which no complete amino acid sequence has been furnished. Regarding applicants comments about the structure of MAdCAM disclosed in the specification, there is no disclosure in the specification as to what particular amino acids can or cannot be substituted wherein the fusion protein would maintain all of the required functions of MAdCAM and there is no disclosure as to what particular amino acids substitutions could be tolerated in any particular section of the sequence with the retention of MAdCAM function.

4. Claims 24-26,28-32,103,105-109,111-113,115,116,118-122,124,125,136-50,152-160 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter

which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants arguments have been considered and deemed not persuasive.

The specification is not enabling for the claimed fusion. Said claims recite that the fusion protein contains an $\alpha 4\beta 7$ integrin-binding fragment and wherein said molecule has a particular degree of similarity with a specific amino acid sequence recited in the claim. The claims encompass a sequence that has the recited sequence similarity and also the functional property of $\alpha 4\beta 7$ integrin-binding. However, there is no disclosure in the specification as to what amino acid residues are important for $\alpha 4\beta 7$ integrin-binding. The claims encompass fusion proteins wherein 45% to 10% of the amino acid sequence has no similarity to the sequence recited in the claim. The art recognizes that even single amino acid change or mutation can destroy the function of the biomolecule in many instances. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence similarity (wherein the entire sequence is not part of the binding domain) results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function. Lederman et al. document this unpredictability of the relationship between sequence and function wherein a single amino acid substitution can ablate receptor/ligand binding. Therefore, it would be unpredictable as to what amino acid sequences would or would not have the functional activity recited in the claim. It would require undue experimentation to practice the claimed invention based on the teachings of the specification.

Regarding the Briskin declaration, said declaration discloses experiments performed after the filing date of the instant invention using techniques not disclosed in the specification. The Briskin declaration also establishes that it was unpredictable prior to having actually performed the experiments disclosed in said declaration as to what residues were actually important to $\alpha 4\beta 7$ integrin-binding and what residues could or could not tolerate substitutions. The claims encompass fusion proteins wherein 45% to 10% of the amino acid sequence has no similarity to the sequence recited in the claim. The art recognizes that even single amino acid change or mutation can destroy the function of the biomolecule in many instances. The effects of these changes are largely

unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence similarity (wherein the entire sequence is not part of the binding domain) results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function.

5. Regarding the priority date of the instant application with regards to the application of prior art, the claimed inventions are not disclosed in parent application 08/386857 and therefore the claimed inventions are not entitled to priority to said application with regards to the application of prior art.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 24-26,28-31,103,105-109,111,113,115,116,118,120-122,124,136-42,144-147,149-150,152,154,155,157-160 are rejected under 35 U.S.C. 103(a) as being unpatentable over Butcher et al. (W0 94/13312) in view of Vonderheide et al. (US Patent 5,599,676) and Erle et al. for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive.

Butcher et al. teach MAdCAM/Ig constant region fusion proteins (see page 7). Murine MAdCAM has a $\alpha 4\beta 7$ integrin-binding fragment. Butcher et al. teach that the peptide is joined to IgG, indicating that the c-terminal of said peptide is joined to the N-terminal of Ig (see page 7). Butcher et al. teach soluble MAdCAM (page 5) and fusion molecules containing said peptide (see page 7). The MAdCAM/Ig fusion protein taught by Butcher et al. contains at least a portion of Ig heavy chain constant region (eg. intact IgG, see page 7). IgG that contains hinge, CH2 and CH3 domains because these regions are found in IgG. The fusion protein taught by Butcher et al. is a "hybrid immunoglobulin". Butcher et al. do not teach primate or human MAdCAM fusion proteins. Erle et al. teach that human MAdCAM binds to $\alpha 4\beta 7$ (see abstract). Erle et al. teach human cell lines expressing $\alpha 4\beta 7$ and MAdCAM (see Abstract). Vonderheide et

al. teach methods to isolate nucleic acids encoding molecules that bind α4β7 (see columns 4-10 and claims) wherein said methods require human cell lines expressing α4β7 and human cells expressing MAdCAM (see Abstract). Vonderheide et al. teach nucleic acids encoding molecules that bind α4β7. Vonderheide et al. teach that such nucleic acids can be used to produce the protein encoded by said nucleic acids (see columns 8-12). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Butcher et al. teach MAdCAM/Ig constant region fusion proteins whilst Vonderheide et al. and Erle et al. provide the means to produce human/primate MAdCAM protein. One of ordinary skill in the art would have been motivated to do the aforementioned because Butcher et al. teach MAdCAM fusion proteins that bind α4β7 can which could have been used for a variety of art recognized purposes.

Regarding applicants comments about In re Deuel, claims 24-26,28-31,103,105-109,111,113,115,116,118,120-122,124,136-42,144-147,149-150, 152,154,155,157-160 do not recite specific amino acid sequences (or nucleic acids which encode a specific amino acid sequence recited in said claim). Said claims are drawn to sequences that would be isolated based on the three known MADCAM nucleic acid molecules disclosed in the specification. The decision in In re Deuel was not address the obviousness of such claims because claims of the scope of claims 24-26,28-31,103,105-109,111,113,115,116,118,120-122,124,136-42,144-147,149-150, 152,154,155,157-160 were not under consideration (eg. all of the claims under consideration were drawn to a specific nucleic acid sequence or a nucleic acid sequence which encoded a specific amino acid sequence recited in said claims). Regarding applicants comments, Vonderheide et al. teach methods to isolate nucleic acids encoding molecules that bind α4β7 (see columns 4-10 and claims). Erle et al. teach that MADCAM binds α4β7 (see abstract and page 525, first column). Regarding applicants comments about the MADCAM experiments in Erle et al., Erle et al. indicate that although their experiments used cells transfected with murine MADCAM, said experiments provide evidence that α4β7 binds human MADCAM because Amany disclose integrins recognize ligands across species (see page 525, first column). Erle et al. also teach a source of human MADCAM nucleic acids (eg. they teach that MADCAM is found in mucosal lymphoid organ HEV and gut lamina propria venules, see page 518, column 1, first paragraph). The method of Vonderheide et al. (US Patent 5,559,676) is

disclosed in claims 1-10 of said patent. Vonderheide et al. (US Patent 5,559,676) is an issued patent and the claims of said patent are presumed enabled. In re Deuel and In re Bell deal with issues related to the degeneracy of the nucleotides encoding for a particular amino acid sequence and the effect that this has on obtaining a particular DNA clone based on amino acid sequence data. Neither case involved teachings of a structurally similar nucleic acid or use of a method recited in claims of an issued US Patent to isolate said structurally analogous molecule. With regards to applicants comments about In re Deuel 34 USPQ2d 1210(Fed. Cir. 1995), the circumstances of In re Deuel differ from the rejection under consideration. In re Deuel deals with issues related to the degeneracy of the nucleotides encoding for a particular amino acid sequence and the effect that this has on obtaining a particular DNA clone based on amino acid sequence data. The method taught by Vonderheide et al. uses $\alpha 4\beta 7$ binding to clone the pertinent molecule, thus overcoming any need for any amino acid data from the protein to be cloned. Furthermore, even with regards to the circumstances surrounding obviousness of DNA based on knowledge of an amino acid sequence, Ex parte Goldgaber 41 USPQ2d 1173 indicates that regarding the issue of whether a method for isolating a DNA molecule makes said molecule obvious, that each case needs to be evaluated on a case by case basis depending on the particular facts in said application. Regarding applicants comments about hindsight reconstruction, Vonderheide et al. teach methods to isolate nucleic acids encoding molecules that bind $\alpha 4\beta 7$ (see columns 4-10 and claims). The method of Vonderheide et al. (US Patent 5,559,676) is disclosed in claims 1-10 of said patent. Vonderheide et al. (US Patent 5,559,676) is an issued patent and the claims of said patent are presumed enabled.

8. Claims 32,112,119,125,143,148,153,156 rejected under 35 U.S.C. 103(a) as being unpatentable over Butcher et al. (W0 94/13312) in view of Vonderheide et al. (US Patent 5,599,676) and Erle et al. as applied to claims 24-26,28-31,103,105-109,111,113,115,116,118,120-122,124,136-142,144-147,149-150,152,154,155,157-160 above, and further in view of Capon et al. (US Patent 5,565,335) for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive.

The previous rejection renders obvious the claimed invention except that the Ig fusion protein is a homodimer. Capon et al. teach Ig fusion protein homodimers (see claim 8). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because the previous rejection renders obvious the claimed invention except that the Ig fusion protein is a homodimer, whilst Capon et al. teach Ig fusion protein heterodimers. One of ordinary skill in the art would have been motivated to do so because homodimeric fusion proteins have a variety of art recognized uses (eg. could be used in immunoassays, etc.).

Regarding applicants comments, the rejection refers to Capon et al. (US Patent 5,565,335). Applicants comments are as per addressed in paragraph 7 of this Office Action.

9. Claims 126-135 are allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ron Schwadron, Ph.D. whose telephone number is 571 272-0851. The examiner can normally be reached on Monday to Thursday from 7:30am to 6:00pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at 571 272 0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. Information regarding the status of an application may be obtained from

the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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